Let’s have a look at a very simple ‘model reaction’:

\[
\text{F} + \text{H-H} \leftrightarrow
\]

We can describe the energy of this system based on the relative position of the atoms. This energy is (in the most simple case) described by the Morse potential:

\[
V(r) = E_{\text{diss}} - \beta (r_r - \sigma)^2
\]

where \( E_{\text{diss}} \) is the respective bond dissociation energy, and \( \beta \) is related to the vibrational energy of the molecule.
Potential Energy Surface

If we put this into a 3-dimensional graph to show the two interatomic distances at the same time, we obtain the “potential-energy surface” for the reaction.

(For systems involving more than 3 atoms, a graphical representation is not possible any more.)
A 2-dimensional projection of this surface is shown at left. The dashed line is the line of minimum (local) energy, which is hence the (most likely) path taken by the molecules. This is also referred to as the “reaction-coordinate pathway”. Plotting the energy along this reaction coordinate $\xi$, we obtain an energy diagram just like the ones we have seen before!

What is the activation energy, what the heat of reaction in this case?

$E_{\text{act}} \sim 4 \text{ kcal/mol}$

$\Delta H_R \sim 34 \text{ kcal/mol}$
Transition State Theory

\[ \text{N}_2\text{O} + \text{NO} \rightarrow \text{N}_2 + \text{NO}_2 \]

- Potential energy (kJ)
  - Reactants: N\(_2\)O(g) + NO(g)
  - Products: N\(_2\)(g) + NO\(_2\)(g)
- Transition state
  - \(E_a\) (forward) = 209 kJ
  - \(E_a\) (reverse) = 348 kJ
  - \(\Delta H = -139\) kJ
Transition State Theory

Reaction Energy Diagram

Reactants: \( \text{BrCH}_3 + \text{OH}^- \)

Transition state: \( \text{Br}^- \text{C} \text{H}_2 \text{OH} \)

Products: \( \text{Br}^- + \text{CH}_3\text{OH} \)

Transition state or 'activated complex'

\( E_a^{(\text{fwd})} \)

\( E_a^{(\text{rev})} \)

\( \Delta H_{\text{rxn}} \)
Transition state theory (also known as 'Activated Complex Theory'), regards the transition state during the reactive event as an activated complex with a very short but finite lifetime. Hence, any reaction can be written as a sequence of reaction steps:

\[
A + B \leftrightarrow \text{(AB)}^\dagger \rightarrow
\]

We can simplify this expression if we assume that the first reaction step is much faster than the second and hence always is at (local) equilibrium (so called equilibrium-step assumption):

\[
\text{...but we also know that } K_{eq} = \exp\{-\Delta G_R/RT\} = \]

\[
C_{AB} = K_{1,eq} C_A C_B =
\]

\[
r_P = k_2 C_{AB} = k_2 K_{1,eq} C_A C_B =
\]
TST, cont’d

We can distinguish two terms in this expression:

- an entropy term, which can be traced back to configurational changes of the reactants to the transition state, and
- an enthalpy change, which represents the energy necessary to break the bond involved in the reaction

Comparison with the usual Arrhenius-expression for the reaction rate constant shows that: \( \Delta H_R^\ddagger \)

It can furthermore be shown from statistical thermodynamics that \( k_2 = k \frac{T}{h} \), where \( k \) is Boltzmann’s constant and \( h \) is Planck’s constant.

From this, we can conclude that - according to TST - a reaction without significant changes in the configuration from the reactants to the transition state (i.e. \( \Delta S_R \approx 0 \)), \( k_0 = kT/h \)

This number is in fact a very good “guessimate” for many reactions, for which the above assumptions holds, such as many unimolecular reactions!
Calculation of $\Delta H^\ddagger = E_f$

Quantum mechanics can be used to find the transition state and compute energies of the reactants and transition complex to give an estimate of the activation energies of the forward and reverse reactions.

Dissociation of CO on the W(111) surface

![Dissociation graph](image)
Femtosecond Laser Spectroscopy

Transition state has a life time of about $10^{-100}$ fs ($\sim$ molecular vibration)

- milli - $10^{-3}$
- micro - $10^{-6}$
- nano - $10^{-9}$
- pico - $10^{-12}$
- femto - $10^{-15}$

1 fs is to 1 second like 1 s is to 32 million years!

(Ahmed Zewail, CalTech, Nobel Prize, Chemistry, 1999)
### Comparison of TST & Collision Theory

**TST:**

\[ r_{\text{TST}} = \frac{kT}{h} \exp\left\{\frac{\Delta S^*_R}{R}\right\} \exp\left\{\frac{-\Delta H^*_R}{RT}\right\} [A] [B] \]

**Collision Theory:**

\[ r_{\text{CT}} = \left\{\frac{8}{\pi} \frac{RT}{\mu}\right\}^{1/2} \pi d_{AB}^2 \exp\left\{-\frac{E}{RT}\right\} [A] [B] \]

- Both theories allow
- Both theories yield
- Both theories show

In fact, non-Arrhenius behavior is quite common in chemical kinetics! Rate constants are often fitted to an expression  
\[ k = B T^n \exp\left\{-\frac{E}{RT}\right\}, \]
where \( B, n \) and \( E \) are effectively empirical fit-parameters!
Where are we...?

• We saw in the last class that collisions between molecules are a necessary prerequisite for a reaction to occur.

• We also saw that the probability that any such collision has sufficient energy to overcome the activation barrier and hence lead to the breaking and/or forming of a chemical bond is dependent on the relative velocity of the collision partners.

• These velocities are described by a Boltzmann distribution, i.e. there is not one fixed velocity that we can assign to any individual molecule participating in the reaction.

\[ p(E) = \exp\left\{-\frac{E}{RT}\right\} \]
So, why can we describe chemical reaction kinetics with (completely deterministic!) differential equations?

In a typical chemical reaction system, we are dealing with VERY LARGE numbers of molecules. Hence, probabilistic fluctuations average out!
Examples...

- Situations in which a more “detailed” look at reactions is necessary:
  - reactions
  - Biomedical
    - even a few
  - Particle engineering
    - crystallization → nucleation!
  - Nanotechnology
    → Calculate the number of molecules in 1 m³ gas at STP.
    → Calculate the number of molecules in a spherical nanoreactor with 100 nm diameter (gas, STP).
    → Calculate the number of atoms in a cubic nanoparticle with a side length of 10 nm.

- Generally: whenever few particles/molecules are involved and fluctuations hence become important!
The Stochastic Approach

• Let’s assume we have a few hundred molecules moving randomly in the gas phase.

• Let’s further assume that these molecules can react according to the following reaction scheme:

\[ A \rightarrow B \]
\[ B \rightarrow C \]

“Conventionally”, we would write the rate law as:

• In the stochastic approach, we now assign ‘reaction probabilities’ to these two events:

\[ r_1 = \]
\[ r_2 = \]

• Note that \( x_j \) are now number of molecules, NOT concentrations! Hence, \( x_j \) represents an integer numbers while \( C_j \) a real. Similarly, \( r_j \) are NOT reaction rates, but reaction probabilities!
The 'Gillespie' Algorithm

• The basic idea:

1. Initialize your system:

2. Compute reaction probabilities $r_j$ for

3. Generate two random numbers $p_1, p_2$ in the interval $[0,1]$.

4. Set the time interval until the next reaction step to $t = -$

5. Use $p_2$ to determine

6. Update simulation

7. Repeat from step #2 until desired final time reached.
'Picking' the Reaction

• Since \( r_1 \) and \( r_2 \) are reaction probabilities, \( r_1/(r_1+r_2) \) describes the relative probability that reaction #1 occurs. This sections the interval \([0,1]\) into stretches with weights proportional to the relative reaction probabilities of the individual reaction steps.

• We now “throw a dart” at this line (i.e. pick a random number in \([0,1]\)), and pick in this way which reaction occurred at this time step.

Note: This means that one reactive event occurred, i.e. the reaction as written in the stoichiometric
Running a Simulation

OK... enough theory... let's DO it!

-> go to puccini.che.pitt.edu/~karlj/Classes/CHE400/

-> download 'stochsim.m'

MATLAB
Hepatitis-B Infection

Covalently closed circular DNA (cccDNA) is a key intermediate in HBV replication and serves as the template for transcription of viral RNA. cccDNA is generated by the repair of relaxed circular replicative HBV DNA (rcDNA) in hepatocyte nuclei, and it provides the template for viral and pregenomic messenger RNA.

- Consider the infection of a cell by a virus
- System model:

\[
\begin{align*}
\text{nucleotides} & \xrightarrow{\text{cccDNA}} \text{rcDNA} \quad (1) \\
\text{nucleotides} + \text{rcDNA} & \rightarrow \text{cccDNA} \quad (2) \\
\text{nucleotides} + \text{amino acids} & \xrightarrow{\text{cccDNA}} \text{envelope} \quad (3) \\
\text{cccDNA} & \rightarrow \text{degraded} \quad (4) \\
\text{envelope} & \rightarrow \text{secreted} \quad (5) \\
\text{rcDNA} + \text{envelope} & \rightarrow \text{virus} \quad (6)
\end{align*}
\]

- Assume:
  1. nucleotides and amino acids are available at constant concentrations
  2. cccDNA catalyzes reactions (1) and (3)
Stochastic Nature is Crucial!

The deterministic model cannot express both cases.

Single (or very few) proteins can either survive and lead to infection of cell, or it can die and no infection occurs. **Deterministic models can only capture one of these cases** (dependent on initial conditions).
Features of the Stochastic Solution

- Due to the random nature of the algorithm, the solution looks 'rough', quite unlike solutions of differential equations!
- Since the simulation is done in terms of number of species (i.e. integer numbers!), the solution is in fact discrete and shows discontinuous jumps in time!
- Nevertheless, even for small numbers of reactants, the general shape of the solution can be recognized, and with increasing number of species the solution becomes an increasingly close approximation of the “classical” solution of the deterministic differential equations.
- Even for small system sizes, the (smooth) deterministic solution can be obtained by averaging the solutions of many stochastic simulation runs.
Pros and Cons of Stochastic Simulations

+ extremely
+ can capture
+ must be used

- still need
- interpretation of
- for large system sizes

Overall, stochastic simulations in (bio)chemical kinetics are a fairly recent development (Gillespie, 1977). They were initially slow to catch on, but have exploded in past decade.

Currently a “hot topic” in kinetics research, particularly in biosystems!